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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/497,591	02/03/2000	Gary L. Nelsestuen	09531-016001	7689

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ELI LILLY AND COMPANY
LILLY CORPORATE CENTER
DROP CODE 1104
INDIANAPOLIS, IN 46285

EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/497,591	Applicant(s) NELSESTUEN, GARY L.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 15-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 and 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

The Response to the Restriction Requirement filed April 30, 2001 (Paper No. 8) and Response and Preliminary Amendment to the Claims filed August 29, 2001 (Paper No. 10) have been entered and considered. The Election of Group 1, claims 8-10, and the species election of protein C or APC having a glycine residue at amino acid position 12, a glutamic acid residue at position 33, and an aspartic acid or glutamic acid at position 34 without traverse is acknowledged. Upon reconsideration of the Restriction Requirement, the examiner has determined that search and examination of the subject matter of Claims 8-14 (drawn to various specific mutants of protein C or APC having enhanced membrane binding affinity and the activity of inhibiting clot formation) presents no undue burden. Therefore, Claims 8-14 will be examined.

Status of the Claims

Claims 1-60 are pending. Claims 1-7 and 15-60 are withdrawn as being drawn to non-elected subject matter. Claims 8-14 will be examined on the merits.

Drawings

The drawings are objected to for reasons cited in the Form PTO-948 attached hereto. Correction is required.

Objection

Claims 8-14 are objected to for depending from non-elected Claim 1. Correction is required.

The examiner notes that Claim 12 contains what appears to be a typographical error in line 2. The claim states "...further comprises *or* a glutamic acid..." (emphasis added). Deletion of "or" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-14 are indefinite as to what sequence the phrase "at amino acid 12" (claim 9), "at amino acid 33" and "at amino acid 34" (claim 10), "at amino acid 35" (claim 11), "at amino acid 36" (claim 12), "at amino acid 11" (claim 13), and "at amino acid 29" (claim 14) refers. There is no reference point for the amino acid position at which the substitution is made. Correction is required.

Claims 8-14 are indefinite for the recitation of "corresponding native vitamin K-dependent polypeptide" in Claim 1. The claim is unclear as to the amino acid sequence to be used as a reference point. For example, does "corresponding native", mean a polypeptide from the same species as the modified polypeptide? If so, then the metes

and bounds of "corresponding native" polypeptide are unclear because there are many different sequence variants of a single protein from a single source and the sequences considered to be "native" would be ever changing as new polypeptides are discovered. Clarification is required such as "relative to a protein C polypeptide having a Gla domain of SEQ ID NO:_".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein C or activated protein C (APC) polypeptide comprising a modified GLA domain, wherein the modified Gla domain comprises at least one substitution that increases membrane binding affinity of said polypeptide relative to a protein C or APC polypeptide of identical sequence except for the substitution, wherein said amino acid substitutions comprise the specifically claimed substitutions at specifically claimed positions as in Claims 9-14, does not reasonably provide enablement for any protein C or APC from any source (human or bovine for example) comprising a GLA domain with any number of substitutions or any positions substituted that has the claimed activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404

(Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 8 is drawn to a protein C or activated protein C (APC) from any source (human or bovine for example) comprising any number of modifications in the GLA domain that enhance membrane binding affinity and activity of the polypeptide.

The specification provides working examples of the specific bovine and human protein C or activated protein C polypeptides with the following mutations (relative to SEQ ID NO:1):

Through sequence comparisons of various members of the Vitamin K dependent protein family, observations of membrane binding of Vitamin K dependent protein family members and a number of specific protein C and APC mutants, the specification proposes a contact site archetype. The model predicts a correlation between membrane affinity and a net negative charge on the residues that are located on the surface of the protein (see Figure 11 and Example 5, beginning at p. 37) and that the closer a member of the protein family approaches this electrostatic pattern, the higher its membrane affinity. Thus, the specification presents a proposed model on which to select specific modifications. However, the model does not appear to make any predictions on protein function (enhanced activity is one of the limitations of the claims). Moreover, the model only addresses substitutions of surface amino acids (particular amino acid positions) to

negatively charged amino acids and does not address making substitutions to any amino acid at any position within the Gla domain.

The state of the art is such that it is acknowledged that amino acid modifications of proteins is unpredictable. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. The instant claims encompass proteins which have any number of amino acid substitutions within the Gla domain. However, the specification does not provide guidance of what amino acids may be changed to increase both membrane binding affinity and activity beyond the amino acid positions at the surface of the protein (as described in the model given in Example 5). Moreover, the specification does not appear to provide guidance as to what amino acids may be substituted other than those that will increase the electronegativity at the protein surface.

The amount experimentation necessary to generate the large number of protein C or APC proteins encompassed by the full scope of the claims and possibly screen same for activity with a reasonable expectation of producing a protein with increased activity would be tremendous. The specification lacks direction/guidance regarding which structural features other than the amino acid positions located on the surface of the protein (the electronegativity sites, see Ex. 5) are required in order to provide the

claimed activity. The working examples are only directed to amino acid substitutions at specific positions to amino acids with increased electronegativity. The nature of modifying proteins to achieve a given activity is complex. The state of the prior art establishes the unpredictability of the effects of mutation on protein structure and function. The claims, which fail to recite any limitations of what positions may be substituted and what type of amino acids may be substituted, are broader than the enabling description. Therefore, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with its full scope would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues, other than the surface amino acids, described in the specification, that may be modified to increase membrane binding and activity. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets the full scope of both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 8, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hashimoto et al. (EP 0 354 504, 1990; Ref. AN of IDS filed Oct. 30, 2001 as Paper No. 5).

Hashimoto et al. teach a protein C hybrid polypeptide wherein the Gla domain has been substituted with the Gla domain of Factor X (FX) (see abstract). The FX Gla domain has a glycine at position 11, a glutamate at position 32, and an aspartate at position 33 corresponding to SEQ ID NO:1 (see p. 11, Table I; Example 5). Protein function is an inherent property of its amino acid sequence (its structure). Therefore, since the hybrid protein of Hashimoto et al. is identical in structure to the claimed protein C proteins, it is inherent that the Hashimoto et al. proteins would have the same activities as those proteins claimed (enhanced membrane binding and activity). Moreover, Hashimoto et al. state that the hybrid protein has more potent inhibitory activity (enhanced activity) against the thrombin generation by Factor Va compared to natural protein C (p. 9, Example 6). Therefore, it appears that Hashimoto et al. meets the limitations of the present claims.

Claims 8, 9, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Wakako et al. (EP 0 296 413, 1988; Ref. AM Of IDS filed Oct. 30, 2001 as Paper No. 5).

Wakako et al. teach a human protein C hybrid polypeptide wherein the Gla domain has been substituted with the Gla domain of bovine protein C (see abstract). Bovine protein C has a glycine at position 11 of SEQ ID NO:1. Protein function is an inherent property of its amino acid sequence (its structure). Therefore, since the hybrid protein of Hashimoto et al. is identical in structure to the claimed protein C proteins, it is inherent that the Hashimoto et al. proteins would have the same activities as those proteins claimed (enhanced membrane binding and activity). Moreover, Wakako et al. indicate that the bovine Gla domain would enhance Ca^{++} binding. Thus, it would be inherent that membrane binding would also be enhanced since the bovine Gla domain has more γ-carboxyl glutamate residues required for complex formation, in the presence of Ca^{++}, with negatively charged phospholipids on the cell membrane (see p. 2, lines 35-36). Wakako et al. state that the disclosed hybrid protein has enhanced activity over that of wild-type protein C (p. 8, lines 11-12 and p. 14, claim 1). Thus, it appears that the claims are anticipated by Wakako et al.

Claims 8, 9, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Smirnov et al. (U.S. Patent No. 5,837,843; Reference AI of IDS filed Oct. 30, 2001 as Paper No. 5).

Smirnov et al. teach a protein C chimeric polypeptide wherein the Gla domain has been substituted with the Gla domain of prothrombin. The Gla domain of

prothrombin has a glycine at amino acid position 11 and a phenylalanine at amino acid position 29 of SEQ ID NO: 1 (see abstract, SEQ ID NO:1 (prothrombin Gla sequence) and SEQ ID NO:2 (protein C Gla sequence)). Smirnov et al. state that the binding affinity of the chimera is greater than wild-type protein C when binding is examined on a phospholipid membrane vesicle devoid of PE (phosphatidyl ethanolamine) (see Col. 10, lines 26-31). Smirnov et al. also state that the chimera exhibits much higher anticoagulant activity than APC on vesicles with or without PE. In plasma, the chimera was much more active than wild-type APC on PE containing vesicles (see Col. 10, lines 38-42). Thus, Smirnov et al. teach protein C polypeptides that are structurally identical and patentably indistinguishable from those of present claims 8, 9, and 14.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
November 16, 2001

Director, TC 1600

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600